

Combinatorial fibronectin and laminin signaling promote highly efficient cardiac differentiation of human embryonic stem cells.

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Public Summary:

Cardiomyocytes (CMs) differentiated from human embryonic stem cells (hESCs) are a promising and potentially unlimited cell source for myocardial repair and regeneration. Recently, multiple methodologies-primarily based on the optimization of growth factors-have been described for efficient cardiac differentiation of hESCs. However, the role of extracellular matrix (ECM) signaling in CM differentiation has not yet been explored fully. This study examined the role of ECM signaling in the efficient generation of CMs from both H7 and H9 ESCs. The hESCs were differentiated on ECM substrates composed of a range of fibronectin (FN) and laminin (LN) ratios and gelatin and evaluated by the fluorescence activated cell scanning (FACS) analysis on day 14. Of the ECM substrates examined, the 70:30 FN:LN reproducibly generated the greatest numbers of CMs from both hESC lines. Moreover, the LN receptor integrin $\beta 4$ (ITGB4) and FN receptor integrin $\beta 5$ (ITGB5) genes, jointly with increased phosphorylated focal adhesion kinase and phosphorylated extracellular signal-regulated kinases (p-ERKs), were up-regulated over 13-fold in H7 and H9 cultured on 70:30 FN:LN compared with gelatin. Blocking studies confirmed the role of all these molecules in CM specification, suggesting that the 70:30 FN:LN ECM promotes highly efficient differentiation of CMs through the integrin-mediated MEK/ERK signaling pathway. Lastly, the data suggest that FN:LN-induced signaling utilizes direct cell-to-cell signaling from distinct ITGB4(+) and ITGB5(+) cells.

Scientific Abstract:

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